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Human Dendritic Cell Immunodeficiencies

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None

Abstract
The critical functions of dendritic cells (DCs) in immunity and tolerance have been demonstrated in many animal models but their non-redundant roles in humans are more difficult to probe. Human primary immunodeficiency (PID), resulting from single gene mutations, may result in DC deficiency or dysfunction. This relatively recent recognition illuminates the *in vivo* role of human DCs and the pathophysiology of the associated clinical syndromes. In this review, the development and function of DCs as established in murine models and human *in vitro* systems, is discussed. This forms the basis of predicting the effects of DC deficiency *in vivo* and understanding the consequences of specific mutations on DC development and function. DC deficiency syndromes are associated with heterozygous *GATA2* mutation, bi-allelic and heterozygous *IRF8* mutation and heterozygous *IKZF1* mutation. The intricate involvement of DCs in the balance between immunity and tolerance is leading to increased recognition of their involvement in a number of other immunodeficiency and autoimmune conditions. Owing to the precise control of transcription factor gene expression by super-enhancer elements, phenotypic anomalies are relatively commonly caused by heterozygous mutations.

Key words:
dendritic cells; primary immunodeficiency; autoimmunity; IRF8; GATA2; IKZF1

The role of Dendritic cells in Immunity and Tolerance

Immunity

As professional antigen presenting cells, the prototypic function of Dendritic Cells (DCs) is to activate and prime naïve helper and cytotoxic T cell responses. T cell receptor (TCR) recognition of cognate antigen in the context of MHC provides specificity. T cell activation is driven by a second co-stimulatory signal generated through the binding of CD28 on the T cell with B7 molecules (CD80 and CD86) on the DC. Cytokine secretion by DCs provides a third signal, triggering specific STAT activation pathways to determine T effector lineage. The specificity of cytokine secretion is determined by recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) on DCs, including Toll-like receptors (TLRs), NOD-like receptors (NLRs) and RIG-I-like receptors (RLRs), a process also resulting in DC activation with up regulation of co-stimulatory and MHC molecules. These processes may be spatially separated, as antigen-laden, activated DCs are able to migrate from peripheral tissues through lymphatics to secondary lymph organs where they interact with T cells.

DCs have a unique ability to phagocytose and present exogenous antigens to $CD8^+$ T cells in the context of MHC Class I, a process termed cross-presentation[1]. Cross-priming of $CD8^+$ T cells occurs when the DCs are activated by PRR ligation or in the presence of T cell help[2], a mechanism important in viral and tumor immunity **(Figure 1)**.

In addition to their critical role in adaptive immunity, DCs play a non-redundant role in innate immunity. Their ability to detect pathogen and elaborate cytokines facilitates the activation of innate immune cells including innate lymphoid cells (ILCs)[3], Natural Killer (NK) cells[4] and neutrophils[5], to limit the spread of pathogens during the initiation of adaptive immune mechanisms **(Figure 1)**.

Tolerance

An alternative outcome of DC:T cell interaction is tolerance (reviewed in [6]). Owing to continuous steady-state migration of tissue DCs to lymph organs[7], this is likely to be the predominant type of encounter in health. In the absence of DC activation, antigen presentation or cross-presentation results in the functional inactivation, anergy or deletion of CD4 or CD8 T cells, respectively([8],[9]). Ligation of T cell associated co-inhibitory molecules including CTLA4 or PD-1 by B7 molecules or PD-L1/L2, provides additional inhibitory signals[10]. DC secretion of inhibitory cytokines, such as TGFβ, triggers up regulation of T cell Foxp3 and generation of regulatory T cells (Tregs)[11], which reciprocally maintain a tolerogenic DC phenotype[12]. Secretion of indoleamine 2,3-dioxygenase (IDO) by DCs contributes to tolerance by depleting tryptophan and causing apoptosis of effector T cells[13]. These mechanisms are important in maintaining peripheral tolerance to self-antigens and commensal microbes but also play a role in thymic central tolerance[14]. In the thymus, migratory DCs present self-antigen from the periphery[15] and resident DCs present blood-derived and tissue-specific antigens from medullary thymic epithelial cells[16], for the elimination of self-reactive T cells and induction of natural Tregs[17].

DC subsets

Similarly to T cells, ‘division of labour’ is provided by the existence of several different types of DC. Due to their expression of particular PRRs and secretion of specialized cytokines, these subsets respond preferentially to pathogens and differentially polarize T cells. This allows a large repertoire of responses to antigenic stimuli in the initiation

and regulation of immunity and tolerance. Flexibility is also conferred by phenotypic and functional plasticity dependent on anatomical location and the microenvironment.
Plasmacytoid DC (pDC) and two subsets of myeloid or conventional/classical DC (cDC) are defined by cross-species gene expression studies and classified in a recent consensus study primarily based on ontogeny, with anatomical location and surface antigen expression added as further refinement[18] **(Figure 2)**.
Human pDC express CD123, CD303 and CD304 but are negative for cDC markers CD11c and CD33. cDC1 are characterized by high expression of CD141, Clec9A, XCR1 and BTLA but lower CD11c, while cDC2 have high levels of CD11c, CD1c, CD2, SIRPA and lower CD141. Heterogeneity has recently been shown within the cDC2[19] and pDC compartments, with the latter containing $CD123^{+}$ cDC precursor cells[20].

DC development and function

Haematopoietic lineage specification, including DC development, is driven by the expression of specific transcription factors (TFs). TFs may act in multiple lineages, at different stages of differentiation, with additional functional roles in mature cells.

Lineage and stage specific control of expression is governed by master TFs and co-activators, acting at promoter and enhancer elements. Precise regulation of expression may be facilitated by a complex structure of multiple enhancers termed 'super-enhancers' (SE)([21],[22]). In contrast to haplosufficient heterozygous variants, single-nucleotide polymorphisms associated with autoimmune diseases in GWAS studies are enriched in SE regions[23]. Similarly, gene mutations causing disease through haploinsufficiency, compared to autosomal recessive mutations, are enriched for SE architecture and more likely to encode transcription factors[24]. TFs with super-enhancer structure may, therefore, be sensitive to gene dosage effects, which result in developmental or functional consequences sufficient to cause disease in the haploinsufficient state.

Dendritic cell specification occurs independently of monocyte development in the steady state. The existing mouse model, whereby DCs develop sequentially through a macrophage-DC progenitor (MDP) and common DC progenitor (CDP), has not been supported by recent work in human[25] and is discordant with contemporary models of haematopoiesis in which lineage priming is observed early in development([26],[27] [28]).

pDC

Differentiation of pDC requires GATA2, PU.1, IRF8, E2-2 (TCF4), ZEB2 and suppression of Id2([29],[30],[31],[32]). pDC are able to respond to viral infection, expressing TLR7 and TLR9 to sense single stranded RNA and double-stranded DNA, respectively[33]. In response, they produce large quantities of type I interferon, mainly IFNα, through IRF7 signal transduction[34]. They can also secrete TNF and IL-6 through NF-κB signaling pathways. pDC are able to prime CD4 T cells[35] but are also able to induce Tregs through the expression of inducible T cell Costimulator ligand (ICOS-L)[36] and IDO[37]. They play a role in humoral immunity through the support of B cell functions[38] including B cell activation and proliferation[39], plasma cell differentiation([40],[41]), class-switching[42] and immunoglobulin secretion[43] **(Figure 2)**.

cDC1

cDC1 lineage specification is dependent on GATA2, PU.1, Id2, BATF3 and high levels of IRF8([30],[44],[45],[46]). cDC1 are specialized for defense against viruses, intracellular pathogens and tumors, through their enhanced ability to cross-present antigen to $CD8^+$ T cells and drive Th1 responses. Antigen cross-presentation is enabled by expression of TLR3 and CLEC9A and co-localisation of these PRRs within early endosomes. Engagement of TLR3 by viral double stranded RNA triggers type I interferon production and antigen cross-presentation[47]. CLEC9A is a necrotic cell receptor, which directs cell-associated antigens into the cross-presentation pathway[48]. Further specialized defenses against intracellular pathogens include the elaboration of IL-12, resulting in Th1 polarization and activation of NK cells to form the IL-12/IFNγ axis **(Figure 2)**. Expression of XCR1 and secretion of CXCL9/10 allows co-ordination of XCL1-producing, CXCR3-expressing activated T and NK cell cytotoxic responses([49],[50]). They also play a role in tolerance, potentiated by the ability to secrete TGFβ[51] and the expression of BTLA, which engages HVEM on T cells to promote CD5 expression and peripheral Treg induction[52].

cDC2

Similarly to pDC and cDC1, cDC2 require GATA2 and PU.1 for development, but lineage specification also requires Zeb2 and IRF4([53],[54],[32]). Heterogeneity has been described in the cDC2 population in both mice and humans. Murine heterogeneity is influenced by tissue site and TF dependence including KLF4 and NOTCH2[55]. Phenotypic and functional heterogeneity in human blood cDC2 has been demonstrated by transcriptomics[56] and surface expression of CD5[19], but the influence of TFs on development has not been elucidated.

cDC2 express a large repertoire of TLRs (TLR2, 4, 5, 6, 8), NLRs, RLRs and lectins, equipping them to respond to a wide range of pathogens. Consequently, they can produce many cytokines, including IFNα, IL-23, IL-1, TNF and IL-8. Unlike their murine counterparts, they are able to secrete large quantities of IL-12 and can cross-present antigen *in vitro* as efficiently as cDC1, when appropriately activated[57]. cDC2 can induce Th1, Th2 or Th17 responses, suggesting functional plasticity *in vivo* **(Figure 2)**. DC Inhibitory Receptor 2+ (DCIR2+) cDC2 have been shown to induce tolerance[58] in mice.

Tissue DCs and Langerhans Cells

In most tissues, populations analogous to blood cDC1 and cDC2 can be distinguished([59],[18]), but pDC are frequently only found in inflammation. In lymphoid tissue, cDC migrating from tissues (migratory DCs) can be distinguished from blood-derived 'resident DCs' by their differential expression of HLA-DR and CD11c([60],[61]). Lymphoid tissue also contains a significant number of pDC, even during quiescence.

Langerhans cells, originating in stratified epithelia and expressing a unique profile of Langerin, CD1a and EpCAM, provided the first example of migratory DC through the identification of phenotypically similar cells in skin-draining lymph nodes[62]. Similarly to tissue macrophages and brain microglia, murine LCs are first seeded in tissue by primitive erythro-myeloid precursors from the yolk sac[63]. They persist by local self-renewal in steady-state[64] but influx of bone-marrow derived monocyte[65] and non-monocyte precursors[66] can be seen following inflammation[67]. LC self-renewal is observed in human limb transplant experiments[68] but replacement by donor-derived cells is seen following haematopoietic transplantation[69]. Establishment of a LC network is dependent on PU.1, RUNX3, Id2[70] and signaling from IL-34, TGFβ or

BMP7[71] (reviewed in[72]). The function of LCs is to maintain tolerance to commensals but detect and respond to pathogens, features which have been demonstrated in murine models and *in vitro*([73],[74],[75],[76]).

Predicted effects of DC deficiency

Murine models of constitutive and inducible DC depletion and lineage-restricted transcription factor knockouts have helped delineate the non-redundant functions of DCs *in vivo*; their roles in different immune responses, defense against pathogens and in tolerance (reviewed in[77]). Selective pressure has maintained many conserved elements of immunity between species[78], although identities of cellular phenotype and function are not always maintained at high resolution.

Simple extrapolation from DC-deficient mice challenged with specific pathogens predicts that absolute DC deficiency would lead to complex immunodeficiencies and immune dysregulation. Lack of DCs should cause deficient NK cell and ILC activation with defective T cell responses due to weak TCR signaling and loss of co-stimulatory support. This in turn should lead to deficient responses to viruses, intracellular pathogens and immunosurveillance to cancer. Impairment of tolerogenic mechanisms would also be predicted to cause autoimmunity or loss of mucosal immune homeostasis.

More subtle effects, or pathogen-specific susceptibity, might be seen in the context of depletion or dysfunction of a particular DC subset. For example, disruption of the IL-12/IFNγ axis associated with loss of cDCs or monocytes would be predicted to compromise immunity to mycobacteria while lack of pDC would adversely affect antiviral and respiratory pathogen responses and reduce B cell support for the development of robust humoral immunity([79],[80]).

Quantitative DC Immunodeficiencies

In the context of PID, DCs may be reduced in number, defective in function, or both. Two syndromes associated with absolute monocyte and DC deficiency have been described; heterozygous *GATA2*([81],[82]) and bi-allelic *IRF8* mutations([83],[84]). A more subtle DC deficiency is associated with heterozygous *IRF8* mutation[83] and *IKZF1* haploinsufficiency(Cytlak et al., 2017 in review) **(Table 1)**.

GATA2 haploinsufficiency

GATA2 is a member of the GATA-binding transcription factor family and is essential for the maintenance of haematopoietic stem cells (HSC). Outside the haematopoietic system, GATA2 is expressed in endothelial cells[85] and the central nervous system([86],[87]). GATA2 haploinsufficiency results in attrition of HSC and progression to myelodysplasia and acute myeloid leukaemia, associated with accumulation of additional genetic defects, commonly monosomy 7, trisomy 8, *ASXL1* or *SETBP1* mutations. In keeping with the observation that monogenic haploinsufficient diseases enrich for transcription factors containing super-enhancer regions[24], *GATA2* possesses a 40kb SE region found at -110kb from the transcription start site. This region is also implicated in the pathogenesis inv(3)/t(3:3) AML where its translocation to the *EVI1* gene results in up regulation of EVI1 but haploinsufficiency of GATA2[88].

There is a wide range of age and phenotypes at presentation but a high penetrance with 90% of carriers showing symptoms by the age of 60yrs. A number of syndromes have described these features including familial MDS/AML, Emberger's (deafness, lymphedema and MDS/AML) and MonoMAC (monocytopenia with mycobacterium avium complex). Extra-hematopoietic effects may manifest as primary lymphoedema, dysmorphia or sensorineural deafness.

Prior to the development of classical MDS/AML, immunodeficiency associated with failure of mononuclear cell differentiation, resulting in dendritic cell, monocyte and lymphoid deficiency (DCML deficiency) in blood and tissues, is recognized in many patients. The failure to replenish lymphocytes from bone marrow results in a predominance of memory or terminally differentiated B, T and NK cells in blood. The presence of plasma cells in tissues, preserved immunoglobulin levels and memory T cells affords ongoing immunity to previously encountered antigens but the ability to mount effective adaptive immune responses to novel pathogens is critically impaired. Interestingly, tissue macrophages and epidermal Langerhans cells are preserved, in keeping with their longevity or independence from bone marrow derived precursors. The decline in mononuclear cells can be tracked over decades, during which there is a predisposition to autoimmunity (hepatitis, erythema nodosum), pulmonary alveolar proteinosis, infections (atypical mycobacteria, herpes virus and fungal pathogens) and cancer, particularly HPV/EBV-driven malignancies **(Figure 3).**
It remains unclear whether DCML deficiency and impaired immunity is an invariant finding or whether MDS/AML can occur de novo, particularly in children.

IRF8 mutation
IRF8, a member of the interferon regulatory factor family, is a haematopoietic TF, also known as interferon consensus sequence binding protein (ICSBP), with important roles in development and the function of mature cells of both myeloid and lymphoid lineages([89],[90],[91]).
Two patients are described with bi-allelic *IRF8* mutations; homozygous K108E mutation[83] and compound heterozygous R291Q and R83C mutations[84]. Both presented in infancy with infective symptoms, proliferation of granulocytes and absent DCs and monocytes. The infant carrying homozygous K108E mutations received neonatal BCG vaccine and presented with BCG-osis. The recently described patient with compound heterozygous mutations presented with recurrent respiratory virus infections from the age of 7 weeks. Both required HSCT at the age of 4 months or 4yrs, respectively.

More detailed studies revealed a complex immunodeficiency with phenotypic and transcriptomic perturbations in multiple lineages. The failure of T cells to elaborate Th1 or Th17 cytokines and reduced maturation of NK and $CD8^+$ T cells likely resulted from insufficient TCR signaling strength in the absence of DCs. This, combined with disruption of the IL-12/IFNγ circuit, contributed to infection with intracellular pathogens including low-virulence mycobacterial, mycoplasma and viral infections. Reduced B cell class switching with low IgA levels were in keeping with the supportive role of DCs in humoral immunity.
Lymphoid cell intrinsic effects of *IRF8* mutations were seen with reduced frequency and complexity of somatic hypermutation in B cells, consistent with the requirement of IRF8 for the germinal center reaction[92]. In the T cell compartment, increased GM-CSF production may have contributed to the granulocyte hyperplasia, driven by the unopposed granulocyte promoting action of C/EBPα, normally inhibited by IRF8 in bone marrow progenitors.
In both affected individuals, developmental delay with intracerebral calcification was observed in the absence of congenital infection. In mouse, IRF8 is necessary for microglial development[93] and/or function([94],[95]) but whether this, dysregulated interferon responses or as yet undefined mechanisms are responsible, is unknown **(Figure 4**).

The murine *IRF8* locus has a SE structure with different elements active in cDC1 and pDC lineages[45], consistent with the requirement for precise control of IRF8 levels to determine DC lineage specification[45]. PU.1 dependent IRF8 auto-activation is necessary for the development of murine CDPs and Batf3 is required to maintain IRF8 auto-activation for cDC1 but not pDC differentiation[45]. Haploinsufficiency of genes controlled by SEs frequently causes a cellular and clinical phenotype. Heterozygous T80A mutations have a modest effect on DC development with apparent preservation of cDC1 and pDC, loss of cDC2 and the appearance of CD11c+CD1c- cells[96]. This unpredicted pattern may represent allele-specific mechanisms not yet elucidated. Additional *IRF8* variants localized to the IAD domain (P224L and A201V) result in subtle effects on cDC1 and pDC but more pronounced effects on NK cell maturation and function[97]. It is highly likely that other *IRF8* variants exist with allele-specific effects on haematopoiesis and immunity.

IKZF1 Haploinsufficiency

IKZF1 (*IKAROS*) is the founding member of the *IKAROS* family of TFs, a key regulator of hematopoiesis and a critical factor in murine lymphocyte and plasmacytoid DC development and function[98]. Human IKZF1 haploinsufficiency has recently been described as a cause of common variable immunodeficiency with attrition of B cells, progressive hypogammaglobulinemia, expanded $CD8^+$ T cells, increased risk of bacterial sinopulmonary infections and autoimmunity([99],[100]). pDC deficiency with expansion of cDC1 and reduced non-classical monocytes is an additional cellular phenotype invariably associated with this mutation[101].

IKZF1 is critical for the activity of super-enhancers at genes required for pre-B cell receptor signaling and differentiation, working with B cell master regulators including EBF1 and PAX5[102]. Targets of IKZF1, identified by CHIP-Seq[103], include *ID2*, suppression of which is necessary for pDC development and *BATF3*, required for cDC1 terminal differentiation. De-repression of these loci due to IKZF1 deficiency is consistent with the observed phenotype of absent pDCs but preserved or expanded cDC1s.

pDC deficiency may contribute to the increased risk of bacterial respiratory infection, commensurate with the role of pDC in prompt bacterial clearance and limitation of inflammation in the lung. Lack of pDC support for B cell function and humoral immunity may exacerbate the B cell attrition and progressive hypogammaglobulinemia, despite the presence of plasma cells in tissues. Reduction of the tolerogenic influence of pDC may permit the development of autoimmunity **(Figure 5)**.

Other disorders associated with pancytopenia

Other primary immunodeficiencies and secondary bone marrow failure syndromes result in dendritic and monocyte deficiency. Mutations in adenylate kinase 2 (*AK2*), causing reticular dysgenesis, result in severe pancytopenia, which includes monocyte, dendritic cell and lymphoid lineages([104],[105]). *CXCR4* mutations, causing WHIM (warts, hypogammaglobulinaemia, infections and myelokathexis), prevent leukocytes leaving the bone marrow, resulting in peripheral deficiency of granulocytes, monocytes and dendritic cells[106]. The functional contribution of antigen presenting cell deficiency to these clinical syndromes has not yet been elucidated.

Functional DC deficiencies

DC dysfunction is present in many immunodeficiency syndromes, either through cell intrinsic effects of the mutation or dysregulation of DC interactions with other cells **(Table 1)**.

Bare lymphocyte syndrome

The lack of antigen presentation in MHC Class II deficiency, or 'bare lymphocyte syndrome type II', caused by mutations in *CIITA*, *RFXANK*, *RFC5* or *RFXAP*, results in failure of adaptive immunity with deficient $CD4^+$ T cell responses and hypogammaglobulinemia with poor specific antibody responses[107]. This SCID-like phenotype is characterized by recurrent bacterial, invasive fungal, chronic viral and intracellular pathogen infections with a life expectancy less than 10 years in the absence of definitive treatment with HSCT[108].

Wiskott-Aldrich Syndrome

A migratory dendritic cell defect is caused by mutations of the *WAS* (Wiskott-Aldrich syndrome) gene, encoding for a cytoskeletal protein. An abnormal DC:Tcell immune synapse results in impaired T cell and antibody responses leading to recurrent bacterial and viral infections and autoimmunity[109]. The reported increase in DC cross-presentation and expansion of $CD8^+$ T cells in WASp knockout mice has not been observed in humans[110].

CD40/CD40Ligand deficiency

Reciprocal expression of CD40 and CD40L facilitates complex cross-talk networks between activated DCs, B- and T-cells. Dependent on the environment and DC subset, CD40 ligation induces activation and cytokine elaboration, driving T helper cell polarization and B cell help. Direct contact with B cells up regulates BAFF and APRIL, inducing B cell class switching and immunoglobulin secretion (reviewed in[111]). CD40 or CD40L deficiency, causes hyper-IgM (HIGM) syndrome types 1 and 3, respectively, with aberrant B cell class switching and recurrent bacterial respiratory infections. However, unlike other causes of HIGM due to B cell intrinsic mutations, CD40/CD40L deficiency results in defective cell mediated immunity and increased susceptibility to opportunistic infections (reviewed in[112]).

Pitt-Hopkin's Syndrome

E2-2 (TCF4) is necessary for murine pDC development[113]. Haploinsufficiency of TCF4 in humans causes Pitt-Hopkin's Syndrome, characterized by abnormal craniofacial and neural development, intellectual disability and epilepsy. This is associated with reduced numbers of pDC with defective IFNα production[29]. The relative preservation of a $CD123^+CD45RA^+CD303^{low}$ population within the $CD123^+$ pDC gate was recently explained by its definition as DC precursor[20]. In contrast to IKZF1 haploinsufficiency, no additional myeloid cell or B cell intrinsic defects have been described. Although not classified as a primary immunodeficiency, one study reported recurrent, commonly sinopulmonary infection in 35% of patients[114].

IRF7 deficiency

IRF7 is necessary for the expression of type I and type III IFN genes in response to virus and is constitutively expressed in pDC[115]. Severe influenza infection and

failure of IFN type I and III production by leukocytes, including pDCs, was found in a patient carrying compound heterozygous mutations in *IRF7*. Peripheral blood pDC numbers were preserved[116].

STAT3 loss and gain of function mutations

STAT3, a member of the 'transducer and activator of transcription' (STAT) TF family, is responsible for cytokine signal transduction to regulate cell cycle, proliferation, differentiation and apoptosis genes. *STAT3* dominant negative mutations cause Hyper IgE syndrome (AD-HIES or Job's syndrome) characterized by facial, dental, skeletal and connective tissue abnormalities, eczematous rashes, recurrent skin and pulmonary staphylococcal and mycotic infections with cold-abscess formation. Defective Th17 responses, due to T cell-intrinsic failure of STAT3 up regulation, are implicated in the pathogenesis. STAT3 is necessary for pDC homeostasis in mouse, required for Flt3 dependent E2.2 expression[117], but pDC numbers were normal in humans with HIES[118]. In contrast, reduction in pDC numbers has been described in *STAT3* gain of function mutations, characterized by diverse symptoms including autoimmunity and lymphoproliferation[119]. Some consequences of aberrant STAT3 function in DCs may be predicted due to its mediation of Flt3 signaling and signal transduction of cytokines involved in often autocrine regulation of DC activation including IL-6[120], IL-10[121], IL-12[122], IL-23[123] and IL-27[124]. The regulatory role of STAT3 in human and murine DCs was supported by the defective tolerogenic responses to IL-10 and increased production of IL-12 seen in STAT3 deficiency([118],[125]).

DOCK8 Deficiency

DOCK8 (dedicator of cytokinesis 8) deficiency also causes hyper-IgE syndrome but is additionally associated with profound lymphopenia and susceptibility to viral infections. Severe pDC deficiency was observed in two patients who successfully cleared progressive oral herpes labialis infection when treated with systemic IFNα 2β[126]. In mouse, NLRP10 deficiency is associated with DC migration defects *in vivo*([127],[128],[129]) but this has not been examined in human.

Hermansky-Pudlak syndrome

Hermansky-Pudlak syndrome is characterized by oculocutaneous albinism, platelet dysfunction and a ceroid storage disorder. A number of types are described, with phenotypic variation related to the underlying genetic mutation. Type 2 is caused by autosomal recessive *AP3B1* mutations and encompasses an immunodeficiency phenotype with recurrent viral and bacterial infections. *AP3B1* encodes for the beta3A subunit of AP-3 (adaptor protein 3) complex, involved in cargo-specific transport of proteins from endosomes to lysosomes. Defects in cytotoxic T and NK cells have been described[130]. Defects have also been shown in CD1-dependent antigen presentation[131], TLR7/9 dependent secretion of type I interferon by plasmacytoid DCs[132] and delayed maturation and cytokine secretion by monocyte-derived DCs[133].

The multi-lineage and multi-level influence exerted by transcription factors and the 'cross-lineage' expression of functional molecules suggests that single gene defects are likely to affect more than one lineage or immune function. DC, lymphoid and myeloid cells all share common origins and the term 'complex immunodeficiency' has

come to denote defects involving multiple immune cells and their functions. Syndromes associated with neutropenic states may result from mutations in genes also found to be important in murine DC development such as GFI1[134] and ELANE[135]. Similarly, genetic mutations implicated in the B- or T- cell dysfunctions of combined or variable immunodeficiencies may affect DC function including TLR3[136], TRAF3[137], ADA[138] or JAK3[139]. Genes with important roles in DC differentiation or function have recently been identified as novel candidate PID-causing genes, based on their biological proximity to known causative genes, through analysis of the 'human gene connectome'([140],[141]).

PID provides the opportunity to interrogate the influence of single genes on DC differentiation and function and the non-redundant roles of DC *in vivo*. Complementarily, recognition of the involvement of DCs in the pathophysiology of PID provides opportunity for novel interventions in these complex syndromes. The central role of DCs in tolerance and immunity, predicts that complex immunodeficiency states involving DCs will continue to feature significantly among newly discovered PID disorders.

Figure 1: DC:T cell interactions

DCs may present endogenous antigen in the context of MHC Class I (MHCI) for presentation to $CD8^+$ T cells, or Class II (MHCII) for presentation to $CD4^+$ T cells. Endogenous or intracellular pathogen-derived proteins undergo cytosolic proteosomal degradation before loading onto MHCI in the endoplasmic reticulum (ER) and transport to the surface. Peptides presented in the context of MHC class II are derived largely through proteolytic degradation in the endosome. These peptides may be derived from exogenous material entering the cell through endocytosis, or endogenous proteins internalized in the endosome by autophagy. Alternatively, DCs may cross-present exogenous antigen in the context of MHCI. Phagocytosis internalizes exogenous antigen into the phagosome where it may be degraded and loaded directly onto MHCI (vacuolar pathway) or exported to the cytosol for proteosomal degradation (cytosolic pathway) and MHCI loading in the ER or re-importation to the phagosome. TLR recognition of pathogen associated molecular patterns (PAMPs) induces the recruitment of signal transduction complexes, the activation of signaling pathways to regulate inflammatory and immune gene sets, elaborate cytokines and up regulate co-stimulatory molecules. Activation of the DC in this way provides co-stimulatory and cytokine driven signals to induce T cell immunity. Recognition of presented antigen by the TCR in the absence of co-stimulation or in the presence of co-inhibitory signals results in T regulatory cell generation or T cell anergy/apoptosis.

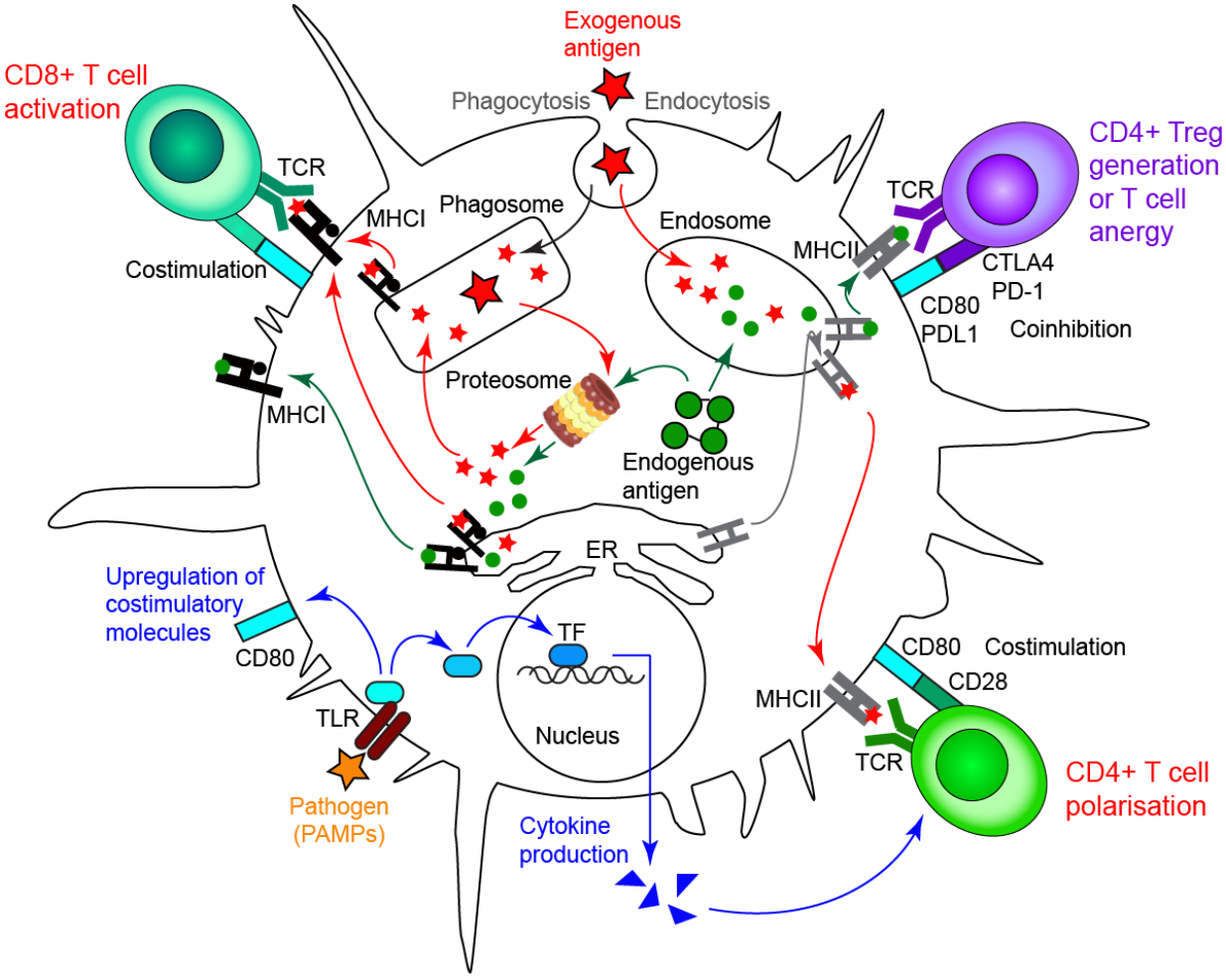

Figure 2: DCs in immunity
Dendritic cells orchestrate the immune response to pathogens and regulate tolerance. Although best known for their initiation of adaptive immunity, they have additional non-redundant roles in innate immunity. Specialized functions, often conferring pathogen-specific immunity, may be performed by particular DC subsets, although likely developmental and functional plasticity exists. Th1 responses and cytotoxic $CD8^+$ and NK cell functions are required for defense against intracellular pathogens and tumor. cDC1 claim specialization for antigen cross-presentation and both cDC1 and cDC2 can elaborate IL-12 to support IFNγ production. Th2 and Th17 responses are more commonly associated with cDC2 activation, which may also result in elaboration of neutrophil chemotractants or stimulants. Heterogeneity exists within the cDC2 population which may include cells developmentally relation to monocytes. Inflammatory monocyte-derived DCs resemble cDC2s by a number of surface markers. pDC are specialized to produce large amounts of anti-viral IFNα and maintain humoral immunity through support of B cell functions.

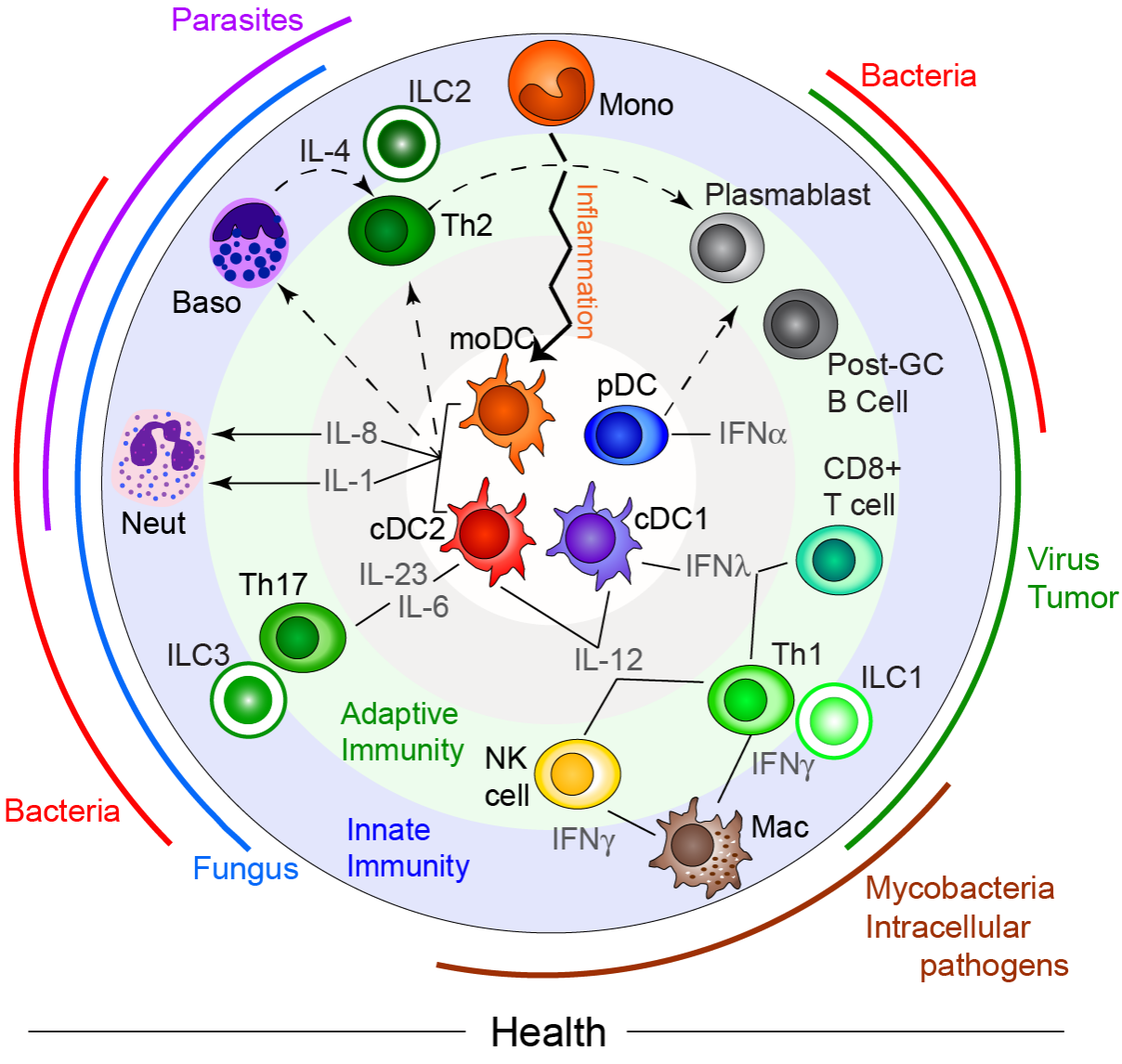

Figure 3: GATA2 deficiency

Heterozygous mutations in *GATA2* result in protean clinical syndromes and symptoms. In the hematopoietic compartment, there is attrition of dendritic cells, monocytes, B and NK cells (DCML deficiency) resulting in a period of immunodeficiency with some immunity maintained by the persistence of memory cells and preservation of tissue macrophages and Langerhans cells. During this phase, symptoms may include autoimmunity (hepatitis, pannicluitis, erythema nodosum), infection with non-tuberculous mycobacteria (MonoMAC syndrome), sino-pulmonary infections, warts, HPV-related neoplasia and pulmonary alveolar proteinosis. There is a high risk of MDS/AML (Familial MDS/AML). Alternative hematopoietic presentations include apparent de novo AML, CMML, aplastic anaemia, autoimmune cytopenias. Extra-hematopoietic effects include sensorineural deafness and primary lymphedema (Emberger's Syndrome: primary lymphedema, deafness and MDS). Absence of cell represents complete deficiency, faded cells represent reduced numbers; red cell outline represents abnormal phenotype or function.

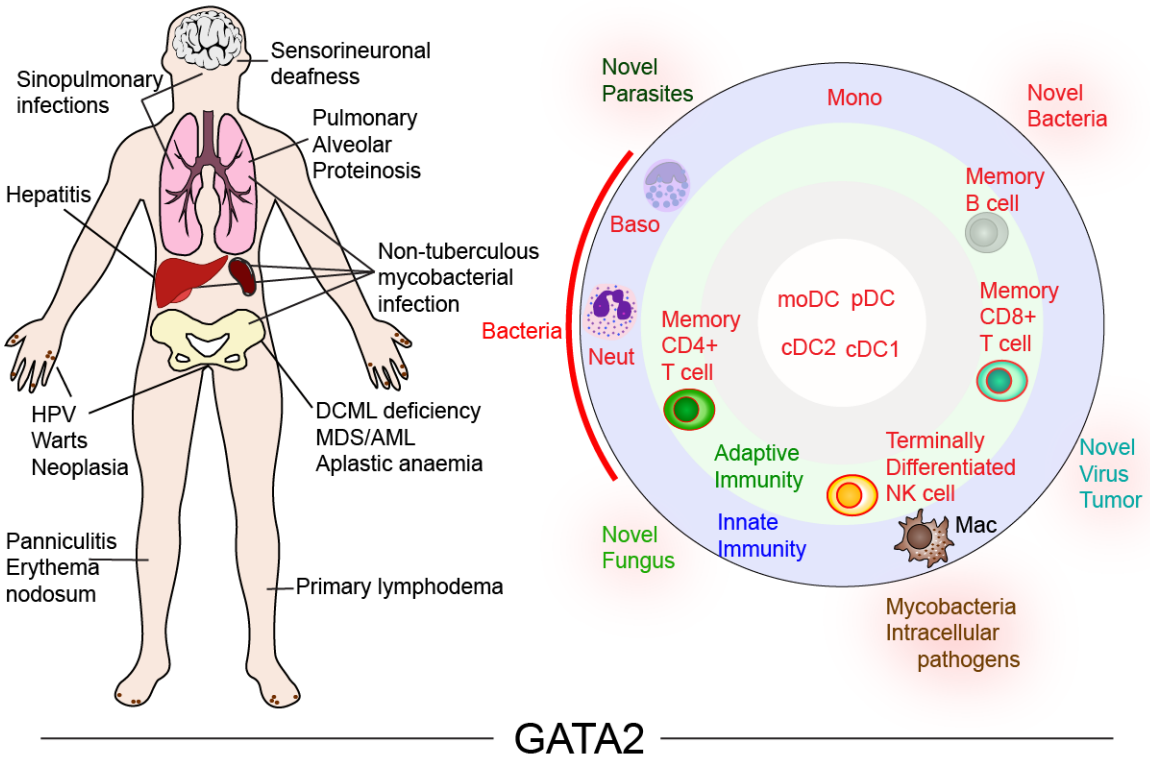

Figure 4: Bi-allelic IRF8 deficiency

The two reported cases carrying bi-allelic *IRF8* mutation presented in infancy with vaccination-related BCG-osis (homozygous K108E mutation) or severe respiratory viral infections (compound heterozygous R291Q and R83C mutations). Proliferation of granulocytes but near absence of monocytes and DCs was observed in both patients. There was a reduction in $CD4^+$ and $CD8^+$ memory cells and deficient Th1 and Th17 T cell responses. There was evidence for reduced somatic hypermutation in peripheral blood B cells and low IgA levels. Tissue macrophages and Langerhans cells were preserved. Absence of cell represents complete deficiency, faded cells represent reduced numbers; red cell outline represents abnormal phenotype or function.

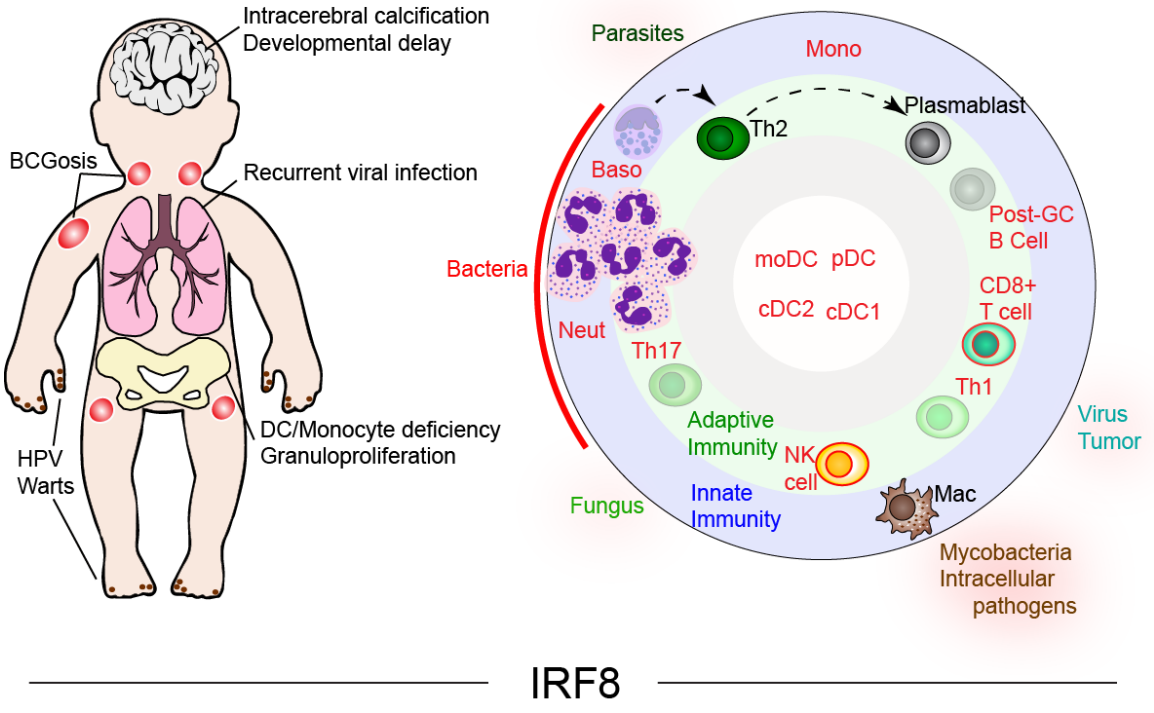

Figure 5: IKZF1 haploinsufficiency

IKZF1 (*IKAROS*) mutation results in a variably penetrant immunodeficiency characterized by progressive attrition of B cells, hypogammaglobulinemia, recurrent bacterial sinopulmonary infections and autoimmunity. In the DC compartment, pDC deficiency but expansion of cDC1 is seen, implicating IKZF1 in the homeostasis of DC subset development. Functional DC defects include failure of IFNα elaboration from pDC and reduced IL-12 production in response to TLR7/8 ligation. Absence of cell represents complete deficiency, faded cells represent reduced numbers; large cell represents expanded numbers, red cell outline represents abnormal phenotype or function.

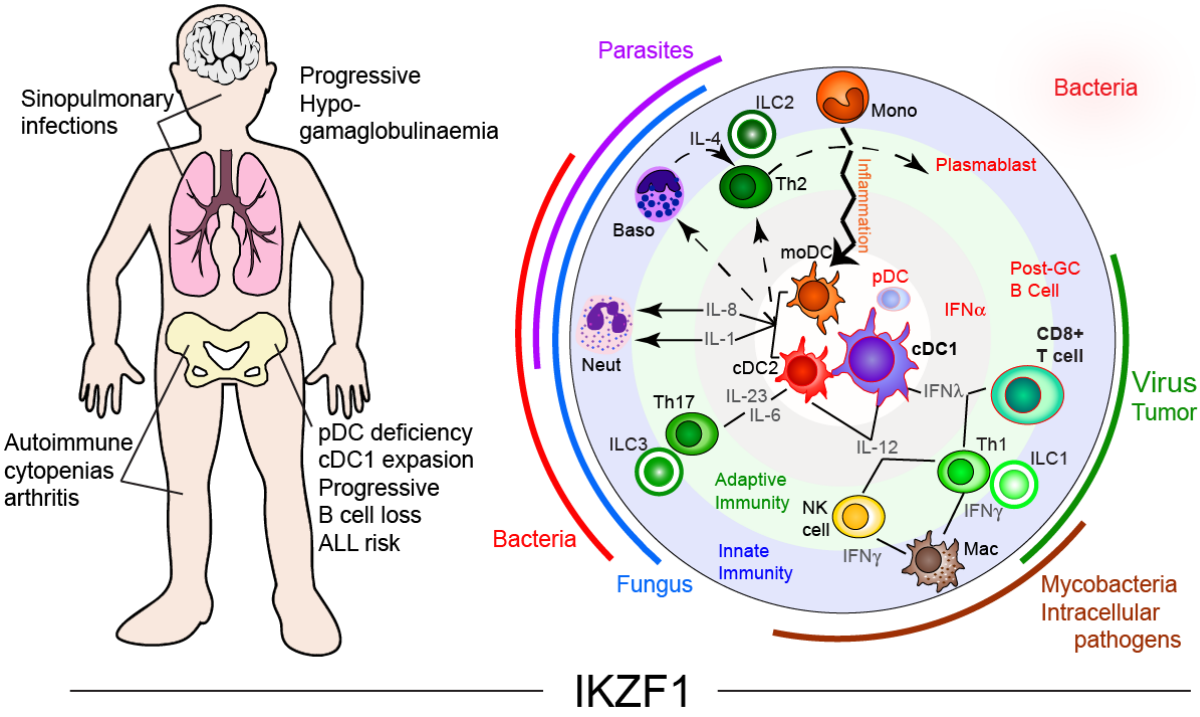

Table 1: Summary of DC deficiencies in PID

Summary of the genetic defects, clinical and cellular phenotypes found in PIDs known to encompass DC deficiency or dysfunction.

	Gene	Clinical phenotype	Cell phenotype	DC Phenotype
Deficiency	Bi-allelic IRF8	Mycobacterial and viral infection Intracerebral calcification and developmental delay	Loss of all monocyte and DC subsets. Impaired Th1 and Th17. Myeloproliferation.	Complete absence of DCs/monocytes but preservation of tissue macrophages and LCs
	Heterozygous GATA2	Mycobacterial, viral (HPV) infection. Lymphodema, deafness, autoimmunity, malignancy, MDS/AML	Denditic cell, monocyte, B and NK lymphoid (DCML) deficiency	Complete absence of DC/monocyte but preservation of tissue macrophages and LCs
	Heterozygous IKZF1	Sino-piulmonary infections, autoimmunity, susceptibility to acute lymphoblastic leukemia	Progressive loss of B cells and immunoglobulins, expanded CD8+ T cells.	Deficient plasmacytoid DCs, expanded cDC1. Reduced IFNa and IL-12 production
Pancytopenia	AK2 (Reticular dysgenesis)	Neonatal fatal septicaemia Hypoplasia of lymphoid organs	Global leukocytopenia	Global loss of monocytes, DCs and LCs
	CXCR4 (WHIM)	Warts (HPV), recurrent bacterial infections, carcinomas	B cell lymphopenia (hypogammaglobulinemia), Myelokathexis with neutropenia	Reduced numbers of monocytes and DCs
Dysfunction	Bare lymphocyte syndrome: MHC Class II deficiency. *CIITA, RFXANK, RFX5, RFXAP mutations*	Failure to thrive, diarrhoea, respiratory tract infections, liver/biliary tract disease	Loss of MHC Class II expression on leukocytes	Deficient antigen presentation and failure to mount effective CD4+ T cell responses
	WASp (Wiskott-Aldrich Syndrome)	Thrombocytopenia, bacterial and viral infections, atopia, autoimmunity, IgA nephropathy, lymphoma	Progressive reduction in T cells	Cytoskeletal protein; affects DC migration and DC:T cell immune synapse. Impaired T cell and antibody responses
	CD40/CD40L	Opportunistic infections. Gastrointestinal and liver/biliary tract disease.	Defective class switching: IgM+ and IgD+ B cells only. Neutropenia	Impaired DC signaling cytokine production and cross-presentation
	TCF4/E2-2 (Pitt-Hopkins Syndrome)	Recurrent infections in 35% of patients. Distinct facial features, epilepsy, intellectual disability	Low IgM	Impaired pDC IFNα responses *in vitro*
	STAT3 gain of function	Lymphoproliferation, autoimmunity (cytopenias and solid organ), infections, short stature	Variable T cell lymphopenia, reduced CD4-CD8-TCRa/b+ T cells	Reduced plasmacytoid DCs
	STAT3 loss of function (Hyper IgE)	Bacterial (S aureus), aspergillus, Pneumocystis jirovecii, mucocutaneous candidiasis, facial, dental, skeletal and connective tissue abnormalities	Reduced B cells, elevated IgE with decreased specific antibodies	Impaired IL-10 responses in DCs
	DOCK8 deficiency (Hyper IgE)	Recurrent infections, cutaneous viral and staphylococcal infections,atopy, susceptibility to cancer	Impaired T cell proliferation, Treg deficiency. Low CD27+ memory B cells, decreased NK cells	Severe pDC deficiency
	Bi-allelic *IRF7*	Severe influenza infection in childhood	No defects reported	Impaired IFN types I and III production from pDC
	Hermansky-Pudlak Syndrome type II (*AP3B1* mutation)	Recurrent viral and bacterial infections	Impaired NK and CD8+ T cell cytotoxicity and degranulation	Defects in CD1 antigen presentation and type I interferon secretion from plasmacytoid DCs

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